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Relative Immaturity in Childhood and Attention-Deficit/Hyperactivity Disorder Symptoms From Childhood to Early Adulthood: Exploring Genetic and Environmental Overlap Across Development

RH = Immaturity and ADHD Across Development

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ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) has been linked to immaturity relative to peers in childhood, yet it is unclear how such immaturity is associated with ADHD across development. This longitudinal twin study examined the genetic and environmental contributions to the association between parent's perception of their child's immaturity relative to peers (RI) in childhood and ADHD symptoms across development.

Method: 1,302 twin pairs from the Twin Study of Child and Adolescent Development (TCHAD) were followed prospectively from childhood to early adulthood. Parent ratings of RI were collected at ages 8-9 and parent and self-ratings of ADHD symptoms at ages 8-9, 13-14, 16-17 and 19-20, using the Child Behavior Checklist Attention Problems (AP) scale. Additionally, ADHD symptoms corresponding to *DSM* criteria were used for sensitivity analysis. Analyses were conducted using longitudinal structural equation modeling with multiple raters.

Results: RI-related etiological factors, predominantly influenced by genes, explained 10-14% of variance in ADHD symptoms between ages 8-9 to 16-17. The influence of these factors on ADHD symptoms attenuated to 4% by ages 19-20. The remaining variance in ADHD symptoms was primarily explained by genetic factors independent of RI, which remained relatively stable across development, explaining 19-30% of the variance in ADHD symptoms from ages 13-14 to 19-20.

Conclusion: Our results show that RI is significantly associated with ADHD symptoms, particularly during childhood/adolescence, and that the association is primarily explained by a shared genetic liability. Nevertheless, the magnitude of associations across development were modest, highlighting that RI is merely one aspect contributing to the complex etiology of ADHD symptoms.

Key words: ADHD; Immaturity; Development; Longitudinal twin analysis

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate symptoms of inattentiveness, hyperactivity, and impulsivity[1]. ADHD has been suggested to be related to a delay in neurodevelopmental maturation[2-5]. Already prior to being described in the *DSM-III*, ADHD was linked to late maturation in observational studies showing that children with ADHD exhibited behaviors that would be normative for younger children, who are naturally more hyperactive, impulsive, and have less developed attentional capacities.[3,6] Further evidence for the role of maturation in ADHD comes from longitudinal studies, showing that whilst 65% of individuals with ADHD in childhood continue to experience impairing symptoms, only around 15% continue to meet full diagnostic criteria by early adulthood.[7] More recently, longitudinal neuroimaging studies have found that ADHD appears related to delayed, but otherwise normal, neurodevelopment[4]. Therefore, although ADHD is a highly heritable disorder showing genetic stability across development,[8,9] some of these genetic effects may be explained by immaturity-related etiological factors.[10] However, there is a paucity of genetically sensitive, longitudinal studies addressing the association between immaturity and ADHD symptoms.

Additionally, several recent studies have shown that children who are born just before school year cut-off, and hence the youngest in their grade, are significantly more likely to be diagnosed with ADHD.[11-14] Although these findings may for some children relate to a delay in neurodevelopmental maturation,[2,11] they have also been proposed to reflect an increased risk of misdiagnosis of ADHD among the youngest children in the school year, owing to parents' and teachers' subjective comparisons of immaturity across children in the same grade.[12] However, not all studies have found an increased risk of ADHD among children who are relatively young for their grade,[15,16] and due to a lack of longitudinal studies, it remains unclear how being young for

one's grade would relate to ADHD in adolescence and adulthood. Assuming that the reported higher rates of diagnosed ADHD among the youngest children in the school year are at least partially explained by comparisons of perceived immaturity across children, it is important to gain a better understanding of how parent-rated immaturity relative to peers contributes to ADHD symptoms across development.[12,17] Considering the age-dependent decline of ADHD symptoms, it seems likely that such immaturity may be more important for ADHD in childhood as compared to adulthood, when maturational differences begin to even out.[2,11]

The aim of the current study was therefore to clarify how relative immaturity, measured by parent ratings in childhood, contributes to ADHD symptoms across development from childhood into early adulthood. Using longitudinal data from the Swedish Twin Study of Child and Adolescent Development (TCHAD)[18], we specifically aimed to answer the following questions: A) How is relative immaturity in childhood related to ADHD symptoms across development and what are the contributions of genetic and environmental factors? B) Are there unique etiological factors that contribute to ADHD symptoms, over and above factors related to relative immaturity? A decreasing association between relative immaturity and ADHD symptoms with age may support the hypothesis that ADHD is, for some children, related to a delay in neurodevelopmental maturation. In parallel, a substantial influence of unique etiological factors on ADHD symptoms, after controlling for relative immaturity, would indicate that ADHD is an etiologically complex disorder where relative immaturity is merely one aspect associated with elevated ADHD symptoms.

METHOD

Sample

TCHAD is a prospective, longitudinal twin study, targeting all 1,480 twin pairs born in Sweden between May 1985 and December 1986, who were alive and living in Sweden in 1994[18].

Twins and their parents were contacted via mailed questionnaires at ages 8-9, 13-14, 16-17, and 19-20 years. Parent ratings were collected at all four time-points (response rate 75%, 73%, 74%, 78%) and twin self-ratings at ages 13-14, 16-17, 19-20 (response rate 78%, 82%, 59%)[8]. In total, 1,302 twin pairs (51% female) contributed to the current study, including 520 monozygotic pairs (MZ), 380 same-sex dizygotic pairs (DZ) and 402 opposite-sex DZ pairs. Zygosity was determined via DNA when available, and otherwise via algorithms derived from discriminant analyses of twins' and parents' responses to validated zygosity questionnaires. Each data collection wave was approved by the ethics committee of Karolinska Institutet, Stockholm.

Relative Immaturity (RI)

There is considerable variation in normal child development, even among children born in the same year. Biological and cognitive measures such as dental status, functional magnetic resonance imaging (fMRI), and formal IQ tests can be useful tools for measuring a child's maturational level. However, such assessments are often not feasible in larger cohort studies. Therefore, relative immaturity in TCHAD was assessed via parent ratings on two items assessed at twins' age 8-9. Item 1 asked parents to estimate their child's level of maturity relative to an average child of the same age on a 5-point scale (1 = very mature, 2 = somewhat mature, 3 = average, 4 = somewhat immature, 5 = very immature). Item 2 asked parents to estimate their child's perceived age, independent of chronological age. Correlation between the two items was 0.75. The variables were standardized and summed to create a continuous measure, with higher scores indicating greater immaturity. The RI measure has been evaluated in two prior studies from our group[19, 20]. Within the TCHAD sample, RI was found to be weakly correlated to early physical maturation (birth weight r_s = .19, age at walking r_s=.10, age at teething r_s=.06) and more strongly correlated to indicators of early mental maturation (ability to handle scissors r_s= .38, ability to tell the time from a watch r_s=.24)[19]. A separate case-control study compared

school children whose parents perceived them as immature to age-matched controls at ages 8-9 and 13-14, and found that RI was related to a more childish body appearance, fine motor function problems, peer problems, and reduced general knowledge[20]. The more immature children also had on average somewhat lower mean Wechsler Intelligence Scale for Children test results (IQ *M*=96.0, *SD*±16.9 vs. *M*=103.6, *SD*±14.5, *p*=.045) and more commission errors in a continuous performance test, suggesting that the RI measure captures aspects of both mental and physical maturation[20]. The RI measure is also significantly correlated with birth month within each year (1985 *r*=0.39/1986 *r*=0.50). In Sweden, all children start school in August the year the child turns seven, meaning that age within the same grade can vary up to 12 months. Children born in December 1986, who were the youngest in their school year, had significantly higher mean RI compared to children born in January. The same was true when comparing children born in December 1985 to those born in May 1985, as data collection in 1985 only included twins born from May onwards (Table S1, available online).

ADHD Symptoms

Parent ratings of ADHD symptoms were collected using the Attention Problem scales (AP) from the Child Behavior Checklist (CBCL)[21] at ages 8-17 and the Adult Behavior Checklist (ABCL) at ages 19-20 [22]. Self-ratings were collected using the AP scales from the Youth Self-Report form (YSR)[23] at ages 13-17 and the Adult Self-Report form (ASR) at ages 19-20[22]. The CBCL, YSR, ABCL, and ASR are empirically derived, standardized questionnaires consisting of similar, developmentally appropriate items for parent and self-ratings of problems experienced in the past six months. All items were rated on a 3-point Likert scale (1 = not true, 2 = sometimes true, 3 = often true) and summed, with higher scores reflecting greater attention problems. The AP scales assess both inattention and hyperactivity problems and have been found to predict ADHD status.[24,25] We therefore consider the AP scales as measures of ADHD symptoms. The

psychometric properties of the AP scales have been evaluated in population-based and clinical samples, with results showing good reliability, as well as convergent and discriminant validity.[21,23] The AP scales were slightly skewed and therefore log-transformed prior to model-fitting, resulting in reduced skewness (mean skew prior to transformation *M*=1.66/after transformation *M*=0.22). As the AP scales are derived via factor analysis, items included vary across ages and rater, with the largest changes between the CBCL/YSR and the ABCL/ASR. Importantly, the CBCL/YSR AP scales contain one item referring to immaturity ("acts too young for his/her age") that is not included in the ABCL/ASR. To avoid this influencing result from the current analysis, the item was removed. Additionally, two alternative definitions of ADHD symptoms were used for sensitivity analyses. Firstly, we used a *DSM*-oriented AP scale based on items from the empirical assessments (CBCL/YSR/ABCL/ASR) that has been judged to be highly consistent with *DSM* diagnostic criteria for ADHD.[26,27] Only items available at each assessment wave were included. Secondly, data collection in TCHAD also included a binary checklist of *DSM-III-r* and *DSM-IV* ADHD diagnostic criteria, rated by parents only. This checklist was used for additional sensitivity analyses, including only symptoms assessed at each assessment wave. The *DSM* ADHD symptoms checklist has previously been described in detail[28]. A full overview of items included in each scale is provided in Table S2 (available online).

Data Analysis

We used a longitudinal twin model with multiple informants to estimate the relative contribution of genetic and environmental factors to covariance between RI and AP across time. Analysis was based on the standard assumptions of the twin method; MZ twins are genetically identical, whilst DZ twins share on average 50% of their segregating genes. With the additional assumption that both types of twins share their environment to an equal extent, the twin method uses the difference in similarity between MZ and DZ twin pairs to decompose variance and

covariance into additive genetic (A), dominant genetic (D), shared environmental (C), and non-shared environmental (E) effects. Although effects of both C and D may be present, they are confounded in the classical twin design and cannot be estimated simultaneously since both parameters are calculated from the differences in twin similarity depending on their genetic relatedness[29].

The current model, illustrated in Figure 1, includes five latent factors, reflecting RI at ages 8-9 (RI_1) and AP at ages 8-9, 13-14, 16-17, and 19-20 (AP_1-AP_4). The factors are indexed by parent ratings (RI_{p1}, AP_{P1}-AP_{P4}) and self-ratings (AP_{s2}-AP_{s4}) when available. Paths λ_p and λ_s indicate the degree to which parent and self-ratings index the factors. As RI was only measured by parent ratings at one time-point, the measured variable RI equals the factor RI_1. Genetic and environmental contributions to RI_1 and AP_1-AP_4 were derived using Cholesky decomposition, where the ordering of variables is important as the first variable takes precedence in explaining variance in subsequent variables. Here, RI_1 was modelled as preceding AP_1-AP_4, with the main focus of the analysis on factors F_1 and F_2. Taking genetic contributions as an example, F_1 reflects RI-related genetic effects that contribute to variance in RI_1 (ages 8-9), as well as explaining variance in AP at ages 8-9, 13-14, 16-17, and 19-20 via paths f_{12}, f_{13}, f_{14} and f_{15}. The second factor (F_2) reflects AP-related stable genetic effects that contribute to variance in AP at ages 8-9, over and above any variance explained by RI_1, as well as contributing to genetic stability in AP via paths f_{22}, f_{23}, f_{24} and f_{25}. Factors F_3-F_5 reflect AP-related innovation genetic effects, referring to newly developing genetic effects in adolescence and early adulthood. F_3 contributes to variance in AP at ages 13-14, F_4 to variance in AP at ages 16-17, and both factors are allowed to explain variance in AP at subsequent time-points via paths f_{34}, f_{35} and f_{45}. Factor F_5 contributes only to variance in AP at ages 19-20 via path f_{55}. The factor structure depicted by F_1-F_5 was implemented for three sources of variance: A, C or D, and E. The model also contains two rater-specific

common factors which capture variance unique to parent ratings (F_p) and self-ratings (F_s) across time, as well as seven rater- and time-specific residuals (R_{P1}-R_{P4}/R_{S2}-R_{S4}). By modeling the residuals, non-shared environmental contributions to the factors can be separated from rater-specific effects. The model has previously been described in detail.[8,30] We also examined qualitative and quantitative sex differences. Qualitative sex differences arise when genetic effects on a phenotype are not the same in males and females. Such differences are estimated by the genetic correlation, r_g, which can vary from zero (i.e. entirely distinct set of genetics factors operating in both sexes) to 1 (identical set of genetic factors operating in both sexes). Quantitative sex differences arise when genetic and environmental factors influence phenotypes to a different degree between sexes. This is modelled by allowing path coefficients to be estimated separately for females and males.

Two sensitivity analyses were conducted. Firstly, we re-ran the full model described in Figure 1, using a *DSM*-oriented AP scale[26, 27]. Secondly, we ran an additional sensitivity analysis using a *DSM* ADHD symptoms checklist. As only parent ratings were available for this measure, parameter estimates were calculated using a standard Cholesky decomposition, without rater-specific factors.

Analyses were performed using the OpenMx 2.0 package.[31] Relevant estimates and 95% profile likelihood confidence intervals were obtained using maximum-likelihood estimation. Model fit was assessed by the Bayesian Information Criterion (BIC), with lower BIC indicating better balance of explanatory power and parsimony.

RESULTS

Descriptive statistics are reported in Table S3 (available online) by age, sex, and rater. Mean parent-rated RI and AP were generally higher in males than females until ages 16-17, after which differences became less pronounced. Mean parent-ratings of AP were consistently lower

than self-ratings. In turn, self-ratings were higher for girls than boys throughout. Table 1 shows the correlations between RI and AP across time and rater. The correlations between RI at ages 8-9 and parent-rated AP from ages 8-20 were significant, of modest to moderate effect size (r=0.11-0.33), and declined with increasing age. The correlations between RI at ages 8-9 and self-rated AP from ages 13-20 were weaker (r = -0.01-0.14) and no longer significant at ages 19-20. Further, within-time, between-rater correlations were moderate (r=0.32-0.39), as were within-rater, across-time correlations (r=0.38-0.54). Finally, cross-time, cross-rater correlations were generally lower (r=0.09-0.29) and declined with increasing time-intervals between assessments.

Twin Analysis

Intra-class twin (ICC, i.e., twin-correlations within-time and trait) and cross-twin, cross-trait, cross-time (CTCT) correlations for RI and AP are presented by age, zygosity, sex, and rater in Table S4 (available online). At nearly all time-points, ICCs were at least twice as large in MZ twin pairs as in DZ twin pairs, indicating substantial genetic influences to RI and AP at each age. CTCTs showed a similar pattern, with higher MZ than DZ correlations, suggesting that genetic factors contribute to the overlap between the RI and AP, as well as to the association in AP across ages. In general, differences between MZ and DZ correlations where more pronounced for parent ratings than for self-ratings.

Model fitting began with a full additive genetic, shared environmental, and unique environmental (ACE) model (Table 2; Model 1), allowing for quantitative and qualitative sex differences and an alternative full additive genetic, dominant genetic, and unique environmental (ADE) model (Table 2; Model 2). The ACE model provided a better fit to the data (ΔBIC = -9.61), and subsequent model simplifications were therefore tested against the ACE model. We started by dropping the quantitative and qualitative sex differences (Table 2; Model 3: ΔBIC = -150.24). We then tested if the C parameter could be constrained to zero. The resulting AE model

with no sex differences (Table 2; Model 4) provided the best fit to the data as indexed by lowest BIC (ΔBIC = -52.26). Standardized parameter estimates for the genetic and environmental factors (F_1-F_5 in Figure 1) are presented in Table 3, together with percentage of the total variance in each factor explained by A (h^2) and E (e^2). Total phenotypic variance in AP explained by genetic and environmental factors across time is also illustrated in Figure 2. RI-related genetic effects (A_1) explained 86% of the variance in RI at ages 8-9. The same RI-related genetic effects also explained a small but stable proportion (7-9%) of the variance in AP between ages 8-17. This effect attenuated by ages 19-20, where RI-related genetic effects only explained 3% of the variance in AP. In contrast, AP-related stable genetic effects (A_2) explained 52% of the variance in AP at ages 8-9 and continued to contribute substantially to AP into adulthood, explaining 30%, 26%, and 19% of the variance in AP at ages 13-14, 16-17, and 19-20. In addition to showing considerable genetic stability, new AP-related genetic effects came online throughout development, with A_3 explaining 45% of the variance in AP at ages 13-14, A_4 explaining 23% at ages 16-17, and A_5 explaining 27% at ages 19-20. In comparisons to genetic effects, the overlap between RI-related non-shared environmental effects (E_1) and AP showed a similar pattern, but was of smaller magnitude. E_1 explained between 3-5% of the variance in AP between ages 8-17; however, the contribution dropped to zero by ages 19-20. AP-related stable non-shared environmental effects (E_2) explained 38% of the variance in AP at ages 8-9, but had little influence on AP at subsequent time-points (0-3%). New non-shared environmental effects came online in adolescence and showed some transmission across ages (8-16%).

Parameter estimates for λ_p/λ_s, F_p/F_s and R_p/R_s are presented in Figure S1 (available online). As per previous findings in the TCHAD sample[8], the cross-informant latent factors (AP_1-AP_4) contributed more to parent-rated than self-rated AP at ages when both were available. Rater-specific common factors contributed more towards self-rated than parent-rated AP and a larger

proportion of self-rated AP was modelled as rater- and time-specific residuals, compared to parent-rated AP.

Sensitivity Analyses

An AE model with no sex differences provided the best fit to the data in both sensitivity analyses. Re-fitting the factor model to a *DSM*-oriented AP scale resulted in similar parameter estimates as the main analysis, although the attenuated contribution of RI on AP at age 19-20 was less pronounced. Parameter estimates are presented in Table S5 (available online). Results from the second sensitivity analysis, fitting a standard Cholesky decomposition to parent-rated *DSM* ADHD symptoms, showed a similar pattern of results, although the contribution of RI to *DSM* ADHD symptoms was weaker. Further, non-shared environmental effects explained less of the variance in *DSM* ADHD symptoms, possibly due to the fact that parent ratings of ADHD are known to produce higher ICCs than self-ratings[32]. Parameter estimates are presented in Table S6 (available online).

DISCUSSION

This longitudinal twin study examined the genetic and environmental contributions to the association between parent-rated relative immaturity in childhood and ADHD symptoms across development**.** We found a small but significant phenotypic association between relative immaturity and ADHD symptoms, which remained of similar magnitude across childhood and adolescence, to then decrease somewhat by early adulthood. Genetic and non-shared environmental factors underpinned the association, although the contribution of shared genetic factors was stronger. Around 10-14% of the variance in ADHD symptoms during childhood and adolescence could be explained by etiological factors related to relative immaturity; however, this effect decreased to around 4% in early adulthood. These results suggest that some of the genetic influences on ADHD symptoms are shared with genetic factors related to relative immaturity[10],

in particular during childhood and adolescence. Although only one possible interpretation, the attenuated association between relative immaturity and ADHD symptoms with age may support the hypothesis that the developmental course of ADHD is, for some children, related to a delay in neurodevelopmental maturation.[2,4,5] Nevertheless, the magnitude of the associations between relative immaturity and ADHD symptoms was small across ages, suggesting that relative immaturity is best viewed as merely one factor among many which contributes to elevated ADHD symptoms.

Although we cannot map our measure of relative immaturity onto markers of neurodevelopment, it can be hypothesized that the shared genetic liability between relative immaturity and ADHD symptoms in childhood and adolescence could be mediated via the neurodevelopmental delay previously reported in longitudinal neuroimaging studies of ADHD.[2 4] Children with ADHD attain peak cortical thickness and surface area 2-3 years later than controls.[4,33] This delay is also evident in normally developing children, where higher levels of hyperactivity/impulsivity have been associated with slower rates of cortical maturation.[34] The attenuated, but still significant, genetic overlap between relative immaturity and ADHD symptoms in early adulthood could in turn be hypothesized to reflect maturation of the pre-frontal cortex, which continues to develop well into the mid-twenties and underpins important executive and attentional functions related to ADHD.[35] Nonetheless, a hypothesized genetic link between our measure of relative immaturity and neurodevelopment trajectories[4,34,36] is merely one possible explanation among many. Another possibility is that our findings reflect birth-month effects, as several previous studies have reported an increased risk of ADHD among children born in the final months before school year cut-off.[12-14] It is therefore possible that the youngest twins within each school year in TCHAD were (incorrectly) rated by parents as having higher ADHD symptoms due to their birth-month–related higher relative immaturity. However, as twins

do not differ in birth-month and the twin method relies on modelling the difference of within-twin pair correlations between MZ and DZ twins, we were not able to explicitly estimate the variance in ADHD symptoms explained by birth-month effects. Nonetheless, it is unlikely that our findings are entirely explained by such effects, as the mean number of ADHD symptoms did not differ significantly between children born early versus late in the school year, although they differed in mean RI (Table S1, available online). These results align with findings from a previous Swedish study, where rates of clinically diagnosed ADHD were higher among individuals born in the final months of the school year, but results showed no corresponding effect of birth-month on ADHD symptom assessed via parent or self-rating.[11] Similarly, a Canadian study of self-reported ADHD symptoms in adults found no differences in symptom levels depending on birth-month.[37] These findings, together with results from the current study, suggest that the reported increased risk of ADHD among children born late in the school year may be limited to clinically diagnosed ADHD in childhood, as birth-month effects do not appear to be strongly related to parent and self-ratings of ADHD symptoms.

In addition to clarifying the genetic and environmental contributions to the association between relative immaturity and ADHD symptoms, results from the current study also highlight that the magnitude of the association was small and that the majority of the variance in ADHD symptoms across all ages is explained by genetic factors independent of relative immaturity. In line with results from previous longitudinal twin studies,[8,9] genetic factors uniquely related to ADHD symptoms showed considerable stability from childhood to early adulthood, as well as the emergence of new genetic factors in adolescence and adulthood. Interestingly, results from a recent twin study suggest that the genetic factors that underpin ADHD symptoms in childhood are largely independent of those contributing to intra-individual differences in developmental trajectories of ADHD symptoms[38]. In parallel, findings from longitudinal neuroimaging studies

have shown that, independently of symptom severity in childhood, remittance of ADHD symptoms is associated with a convergence toward normal neurodevelopment, whereas persistence appears linked to atypical trajectories of fixed or accelerated cortical thinning and reduced volumes of the subcortical, inferior-posterior cerebellar lobes[36]. It is possible that our results map onto these suggested partly distinct developmental processes, as relative immaturity-related genetic effects were more important in childhood/adolescence and showed attenuation with increasing age, whilst AP-related genetic effects showed both considerable stability across development and innovation during adolescence and early adulthood. However, this pattern of results could also be due to changes in the AP scales across ages. The AP scales based on the ABCL/ASR include fewer hyperactive-impulsive symptoms and more items related to problems with attention, memory, and executive function, compared to the CBCL/YSR. Additionally, some of the items in the AP scales are not specific to ADHD. To test the impact of these changes on our findings, two sensitivity analyses using alternative measures of ADHD *DSM* symptoms were conducted, including only item available at each assessment wave. Findings from both analyses showed an association between relative immaturity and ADHD symptoms, which attenuated with age, and the emergence of new ADHD-related etiological factors in adolescence/adulthood. This suggests that results from the current study are not merely artefacts of changes in the AP scales over time. Nonetheless, the sensitivity analysis using a parent-rated *DSM* ADHD symptom checklist did show an overall weaker association between relative immaturity and ADHD symptoms across development. However, this analysis relied on parent ratings only. This may be problematic since self-ratings of ADHD symptoms are likely to become an increasingly important source of information during the transition from childhood into adolescence/adulthood. Additionally, previous twin studies have demonstrated that estimates of genetic and environmental influences on behavior partly depend on the type of rater information used, and

that estimates based on both parent- and self-ratings are likely to be less biased by rater-specific effects compared to results relying on only one rater.[8,32]

Our results must be interpreted in light of the study limitations. First, our measure of relative immaturity relies on parent ratings on two items in childhood. We can therefore not comment on the stability of RI into adolescence, the relationship with cognitive measure such as IQ, nor on the exact type of maturation that our measure of RI captures. Nevertheless, a recently published study found that 74% of parents to children with ADHD and intellectual disabilities were able to estimate their child's development age within 15 points (i.e. one standard deviation) of their child's measured IQ. Similar to the RI measure used in the current study, assessment of developmental age was based on one parental question ("At what developmental age do you think your child is functioning?")[39]. These findings suggest that parent ratings can provide meaningful information regarding a child's maturational level. Second, participation rates at ages 19-20 were lower than at previous assessments waves. Non-responders were more likely to be male and have higher rates of ADHD symptoms in childhood, meaning that ADHD symptoms at age 19-20 may be truncated at the extreme. This, the use of parent- and self-rated ADHD symptoms may mean that our findings are not directly generalizable to clinically diagnosed ADHD. However, there is considerable evidence that ADHD represents the extreme end of traits that are continuously distributed in the population and underpinned by a similar etiology[40]. The use of prospectively collected, longitudinal data from multiple raters also affords this study several strengths: we were able to estimate stability and innovation of etiological factors across development,[30] and the use of multiple raters allowed us to model measurement error, rater effects, and non-shared environmental effects separately, thus reducing the influence of rater-specific effects on the genetic and environmental parameter estimates.[8,30]

Findings from the current study contribute to the ongoing and somewhat polarized debate,

where ADHD on the one hand is conceptualized as a maturational delay that children will eventually outgrow, and on the other hand, as a chronic neurodevelopment disorder with no relationship to immaturity.[41] Our results challenge these simplistic views and highlight that perceived relative immaturity is indeed associated with ADHD symptoms, particularly during childhood and adolescence, and that this is primarily due to a shared genetic liability. Nonetheless, the majority of variance in ADHD symptoms at all ages was explained by immaturity-independent etiologic factors, suggesting that parental perceptions of immaturity are unlikely to be a major etiological marker of ADHD and are better viewed as merely one aspect among many associated with elevated levels of ADHD symptoms. Future research will need to consider complex etiological models when studying ADHD across the lifespan. Research aimed at understanding the pathophysiological mechanisms that mediate the etiological overlap between relative immaturity and ADHD symptoms might benefit from genetically sensitive, longitudinal data incorporating measures of both perceived (by parents/teachers) and biological maturation (e.g. fMRI). An increased understanding of the association between relative immaturity and ADHD symptoms is also of clinical relevance, as the risk of misclassification of ADHD due to subjective comparisons of immaturity among children in the same school year must be weighed against the possibility that immaturity and ADHD symptoms in childhood are partly explained by common etiological factors.

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Figure 1: Longitudinal Cholesky decomposition with multiple informants, presented for one source of variance, such as additive genetic effects. Note: The model contains five latent factors for relative immaturity (RI: RI_1) and attention problems (AP: AP_1) to AP_4, reflecting the "shared" view of attention problems (AP) at each age. Latent variables are indexed by parent ratings (P) and twin self-ratings (S) when available. The degree to which parent and self-ratings index the latent factors is indicated by the paths λ_P and λ_S. Since RI was only rated by parents at age 8-9, the latent factor equals the measured variable. F_P and F_S reflect rater-specific latent common factors for parent and self-ratings. R_P and R_S refer to rater- and time-specific residuals for parent and self-ratings. The genetic and environmental influences on RI_1 and AP_1 to AP_4 are modeled using Cholesky decomposition. See the "Data Analysis" section and "Results" section for further details.

Figure 2: Proportion of total variance in attention-deficit/hyperactivity disorder (ADHD) symptoms accounted for by relative immaturity (RI)-related and attention problems (AP)-related etiological factors from childhood to early adulthood, presented separately for genetic factors and unique environmental factors. Note: Results from the best-fitting additive genetic and unique environmental model with no gender differences are presented for genetic factors in the upper panel (A) and non-shared environmental factors in the lower panel (B). The y-axis represents the total phenotypic variance in ADHD symptoms accounted for by RI-related and AP-related etiological factors from childhood to early adulthood (ages 8-9 until ages 19-20, on the x-axis). RI corresponds to RI-related etiological effects (F_1 in Figure 1) and AP corresponds to AP-related etiological factors across ages (F_2-F_5 in Figure 1).

Figure S1: Standardized parameter estimates for best-fitting additive genetic and unique environmental model with no gender differences.

Table 1. Pearson's Correlations Between Relative Immaturity (RI) and Attention Problems (AP) Across Rater and Time

Age			8-9		13-14		16-17		19-20	
	Rater		Parent		Parent	Self	Parent	Self	Parent	Self
			RI	AP	AP	AP	AP	AP	AP	AP
8-9	Parent	RI	1.00	0.33	0.29	0.14	0.21	0.11	0.11	-0.01*
	Parent	AP		1.00	0.54	0.25	0.45	0.17	0.39	0.09
13-14	Parent	AP			1.00	0.38	0.61	0.29	0.49	0.20
	Self	AP				1.00	0.32	0.54	0.28	0.38
16-17	Parent	AP					1.00	0.39	0.55	0.18
	Self	AP						1.00	0.28	0.45
19-20	Parent	AP							1.00	0.32
	Self	AP								1.00

Note: Non-significant correlations marked *; all other correlations significant at $p < .001$.

Table 2. Model Fitting Results for Relative Immaturity (RI) and Attention Problems (AP) in a Longitudinal Twin Model With Multiple Informants

Model	Compared With Model	Description	AIC	BIC	Δ BIC	-2LL	Δχ2 (Δ *df*)	*p*
1		Full ACE Mod	1176.12	29833.23	na	29216	na	na
2		Full ADE Mod	1166.51	29842.84	9.61	29225	9.62(0)	na
3	1	ACE, no sex diff	1192.05	29682.99	-150.24	29332	116.07(66)	< .001
4[a]	3	AE, no sex diff	-1213.79	29630.73	-52.26	29340	8.26 (15)	.913

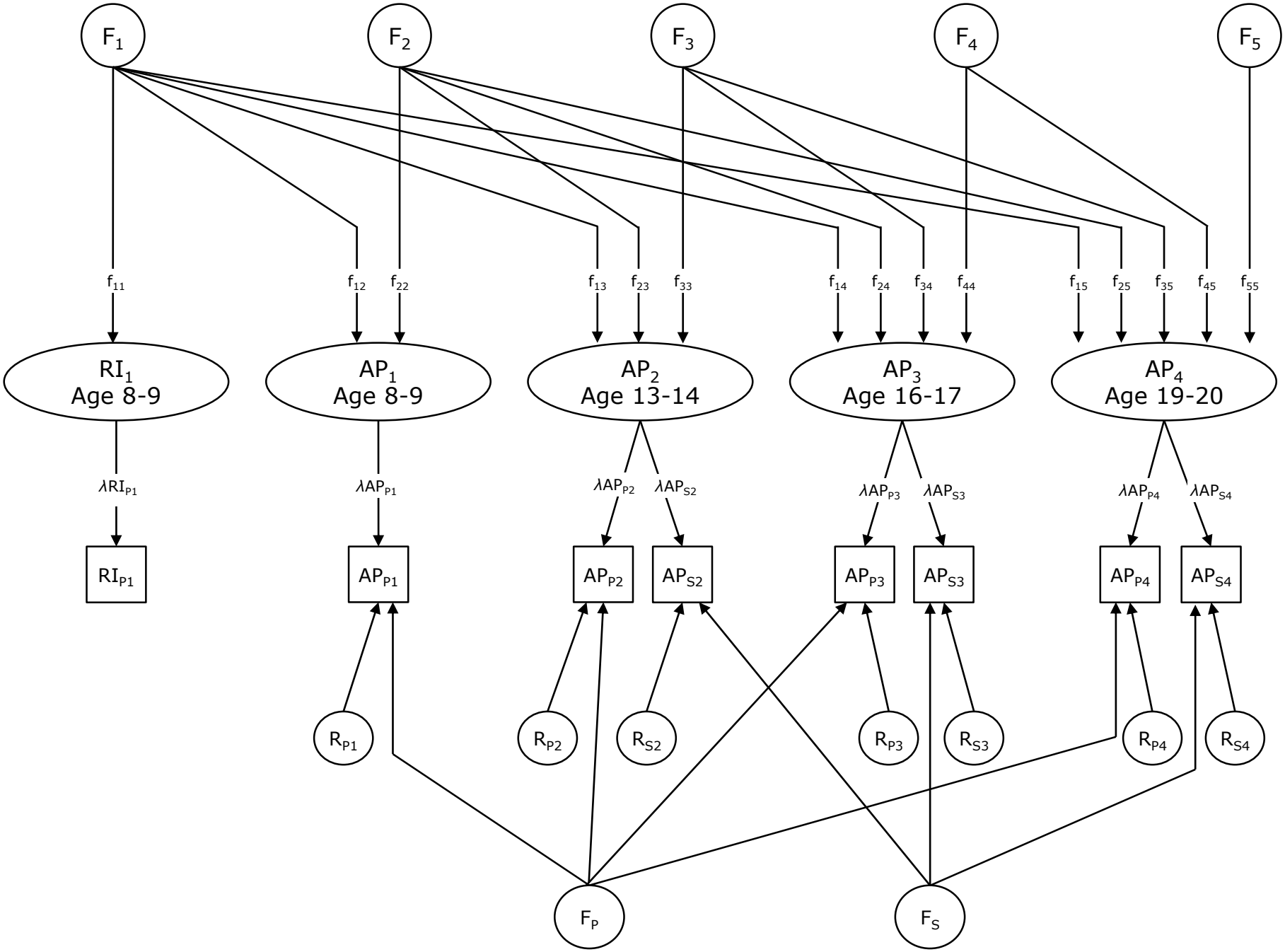
Note: ACE = additive genetic, shared environmental, and unique environmental; ADE = additive genetic, dominant genetic, and unique environmental; AE = additive genetic and unique environmental; BIC = Bayesian information criterion; Full Mod = full model including qualitative and quantitative sex differences; LL = log likelihood; na = not applicable; No sex diff = restricted model with sex no differences.

[a] Best-fitting model.

Table 3. Standardized Parameter Estimates With 95% CIs for Additive Genetic and Unique Environmental Model and Percent of Variance Explained in Latent Factors

	Genetic Parameter Estimates						Non-shared Environmental Parameter Estimates					
Factor/age	Total h2 %	A1	A2	A3	A4	A5	Total e2 %	E1	E2	E3	E4	E5
RI	86%	0.93					14%	0.38				
ages 8-9		(0.91-0.94)						(0.35-0.42)				
		86%						14%				
AP	58%	0.26	0.72				42%	0.20	0.62			
ages 8-9		(0.20-0.33)	(0.68-0.77)					(0.14-0.27)	(0.56-0.66)			
		7%	52%					4%	37%			
AP	84%	0.30	0.55	0.67			16%	0.22	0.18	0.29		
ages 13-14		(0.23-0.36)	(0.48-0.61)	(0.62-0.72)				(0.15-0.28)	(0.12-0.30)	(0.20-0.37)		
		9%	30%	45%				5%	3%	8%		
AP	78%	0.27	0.51	0.44	0.50		22%	0.17	0.04	0.40	0.15	
agea 16-17		(0.20-0.34)	(0.42-0.59)	(0.35-0.53)	(0.41-0.58)			(0.10-0.24)	(-0.05-0.15)	(0.30-0.50)	(-0.01-0.31)	
		7%	26%	20%	25%			3%	0%	16%	2%	
AP	77%	0.17	0.44	0.30	0.45	0.51	23%	0.08	0.09	0.25	-0.39	0.00
ages 19-20		(0.09-0.25)	(0.30-0.59)	(0.19-0.40)	(0.30-0.60)	(0.33-0.64)		(-0.01-0.17)	(0.01-0.20)	(0.10-0.40)	(-0.54-0.14)	(-0.49-0.49)
		3%	19%	9%	20%	26%		1%	1%	6%	15%	0%

Note: A1-A5 and E1-E5 show latent factors presented separately for genetic and non-shared environmental effects (see Figure 1). 95% profile likelihood confidence intervals are presented in parentheses. AP = attention problems; e2 = total proportion of variance explained by non-shared environmental factors; h2 = total proportion of variance explained by genetic factors; RI = relative immaturity.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Age 8-9
AP1
Age 8-9
AP2
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AP3
Age 16-17
AP4
Age 19-20
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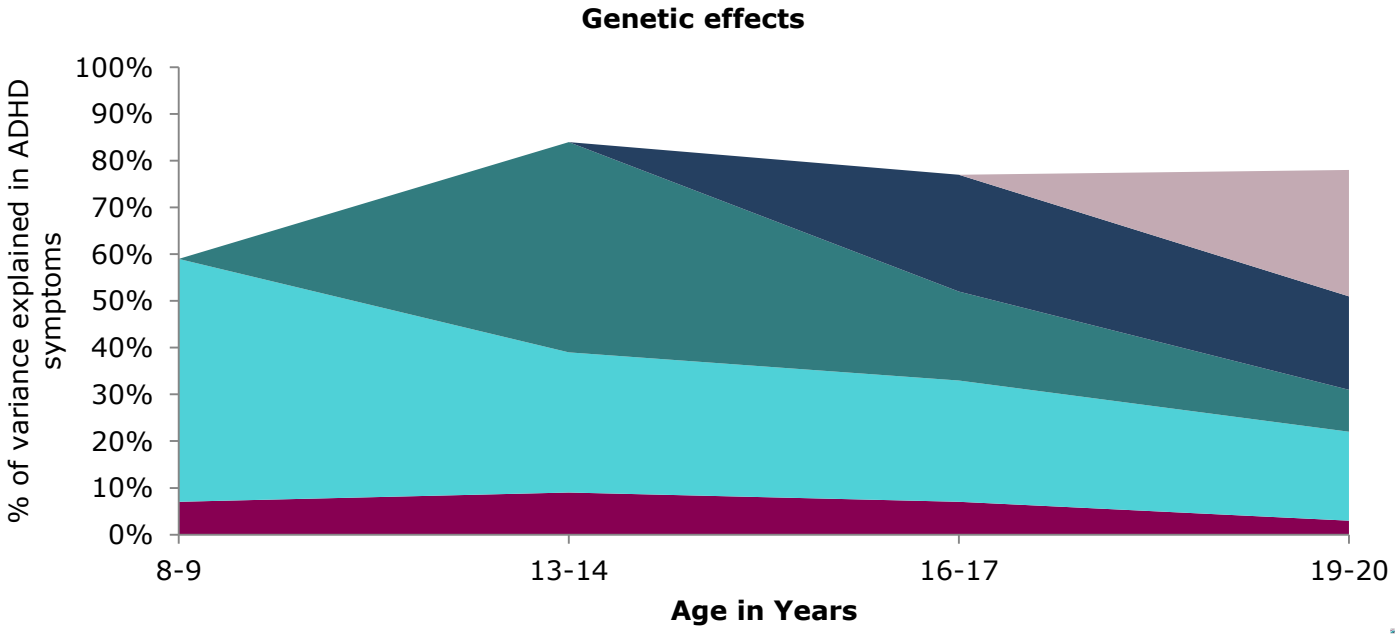
Genetic effects
% of variance explained in ADHD symptoms
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
8-9
13-14
16-17
19-20
Age in Years

B

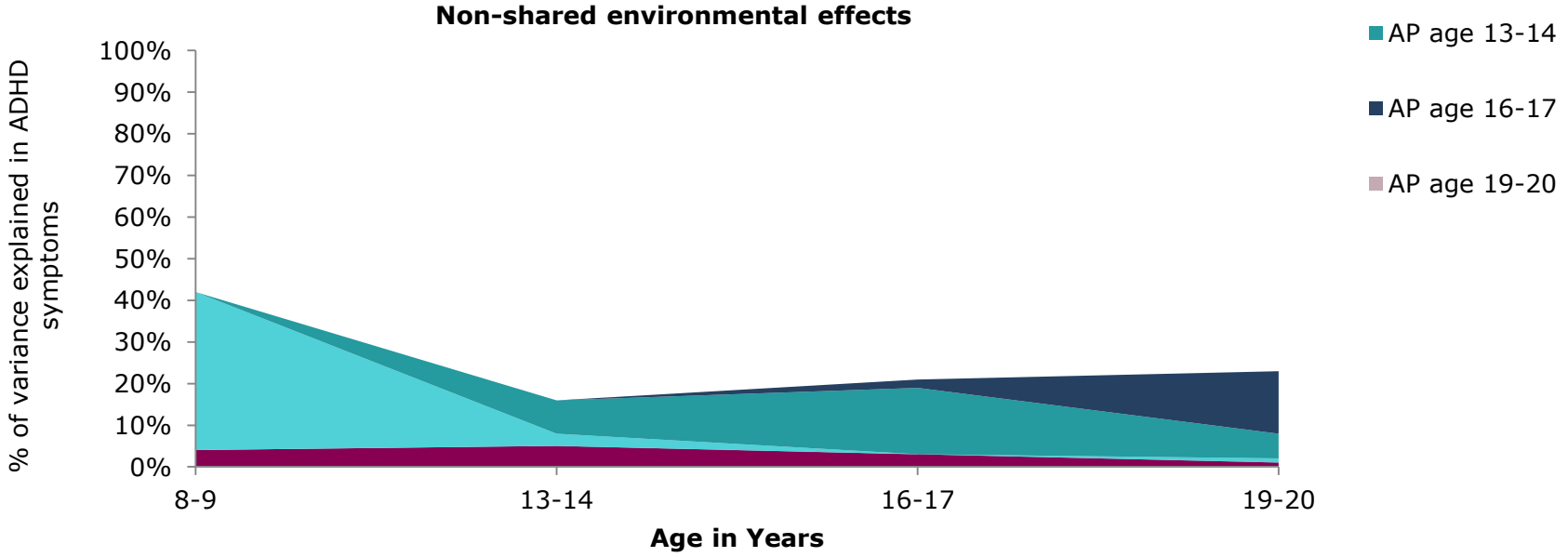
Non-shared environmental effects
% of variance explained in ADHD symptoms
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
8-9
13-14
16-17
19-20
Age in Years
RI age 8-9
AP age 8-9
AP age 13-14
AP age 16-17
AP age 19-20

Table S1. Means (Standard Deviations [SD]) and T-Test Statistics of Mean Differences in Relative Immaturity (RI) and Attention Problems (AP) for Twins Born Early Versus Late in the School Year

	1985						
	May		Dec		Test Statistic		
	M	**SD**	**M**	**SD**	***t***	***DF***	***p***
RI_{p1}	-0.72	1.88	1.39	1.70	-8.00	192	<.001
AP_{p1}	1.10	1.61	1.61	2.11	-1.95	202	.053
AP_{p2}	0.78	1.41	1.04	1.73	-1.20	202	.232
AP_{p3}	0.55	1.36	1.11	1.53	-2.67	188	.008
AP_{p4}	2.30	2.81	2.74	2.86	-0.77	95	.441
AP_{s2}	3.19	2.46	3.04	2.18	0.46	205	.647
AP_{s3}	3.16	2.60	3.40	2.56	-0.67	213	.506
APs_4	5.63	3.99	4.53	3.55	1.77	149	.080
	1986						
	Jan		Dec		Test Statistic		
	M	**SD**	**M**	**SD**	***t***	***DF***	***p***
RI_{p1}	-1.66	1.53	1.19	1.68	-12.45	194	<.001
AP_{p1}	1.18	1.65	1.45	2.10	-1.06	214	.292
AP_{p2}	0.93	1.65	1.31	1.99	-1.53	208	.129
AP_{p3}	0.94	1.62	1.29	1.94	-1.47	218	.143
AP_{p4}	3.29	4.05	3.05	4.13	0.31	119	.755
AP_{s2}	3.26	2.56	3.19	2.36	0.23	218	.819
AP_{s3}	3.67	2.37	3.47	2.50	0.61	227	.544
AP_{s4}	6.42	4.59	5.30	4.46	1.57	164	.119

Note: Results are presented by birth year. For 1985, comparisons are made between twins born in May and December, as data collection in 1985 only included twins born in May onwards. For 1986, comparisons are made between twins born in January and December. AP_{p1}-AP_{p4} = parent-rated attention problems assessment wave 1 to 4; AP_{s2}-AP_{s4} = twin self-rated attention problem assessment wave 2 to 4; RI_{p1} = parent-rated relative immaturity assessment wave 1.

Table S2. Items Included in Each Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Assessments Scale Across Wave 1-4

Attention Problems Scale Wave 1 to 3 (Ages 8 to 17)	**CBCL**	**YSR**
Can't concentrate, can't pay attention for long	X	X
Can't sit still; restless, or hyperactive	X	X
Confused or seems to be in a fog	X	X
Daydreams or gets lost in his/her thoughts	X	X
Impulsive or acts without thinking	X	X
Nervous, high-strung, or tense	X	X
Nervous movements or twitching	X	NA
Poor school work	X	X
Poorly coordinated or clumsy	X	X
Stares blankly	X	NA

Attention Problems Scale Wave 4 (Ages 19 and 20)	**ABCL**	**ASR**
Can't concentrate, can't pay attention for long	X	X
Confused or seems to be in a fog	X	NA
Daydreams or gets lost in his/her thoughts	X	X
Poor work performance	X	X
Is too forgetful	X	X
Too dependent on others	X	X
Has trouble planning for the future	X	X
Fails to finish things he/she should do	X	X
Has trouble setting priorities	X	X
Has trouble making decisions	X	X
Passive or lacks initiative	X	NA
Stays away from job even when not sick/on vacation	X	X
Underactive, slow moving, or lacks energy	X	X
Is disorganized	X	X
Tends to lose things	X	X
He/she is not good at details	X	X
Tends to be late for appointments	X	X

***DSM*-Oriented Attention Problem Scale Wave 1 to 4 (Ages 8 to 20)**
Can't concentrate, can't pay attention for long
Can't sit still; restless, or hyperactive
Impulsive or acts without thinking
Nervous movements or twitching

***DSM* ADHD Symptoms Checklist Wave 1 to 4 (Ages 8 to 20)**
Is easily distracted by other events during schoolwork/play

Appears as if he/she is not listening
Lacks endurance
Can never wait for his/her turn
Plays completely unorganized
Can never sit still
Is always on the go, as if he/she is driven by a motor
Has great difficulty sitting still—is very restless (ants up their pants)
Blurts out answers to questions before they have been completed
Has difficulties understanding and following instructions
Cannot play calmly and quietly
Talks all the time
Interrupts and intrudes on others or interferes in other children's games
Loses, forgets, or misplaces things that are important to him/her at school or at home (e.g., toys, school books)

Note: ABCL = Adult Behavior Checklist; ADHD = attention-deficit/hyperactivity disorder; ASR = Adult Self-Report; CBCL = Child Behavior Checklist; NA = not available; YSR = Youth Self Report.

Table S3. Mean (SD) Scores of Relative Immaturity (RI) and Attention Problems (AP) by Age, Rater, Sex, and Zygosity

Rater	Zygosity/Sex	RI_1	AP_1	AP_2	AP_3	AP_4
Parent report	**MZm**	0.37 (1.70)	1.42(93)	0.93(1.45)	0.74(1.34)	2.57(2.94)
	MZf	0.14(1.79)	1.05(1.73)	0.86(1.48)	0.81(1.38)	2.73(3.11)
	DZm	0.21(1.82)	1.57(2.07)	1.21(1.87)	0.97(1.64)	3.21(3.55)
	DZf	-0.18 (1.81)	1.07(1.75)	0.89(1.54)	0.90(1.53)	2.95(3.59)
Child report	**MZm**	NA	NA	2.96(2.38)	2.62(2.22)	4.51 (3.81)
	MZf	NA	NA	3.24(2.38)	3.45(2.44)	5.63 (4.14)
	DZm	NA	NA	3.19(2.48)	3.01(2.44)	4.92 (3.96)
	DZf	NA	NA	3.45(2.48)	3.81(2.57)	6.20 (4.42)

Note: Descriptive statistics reported for the raw, untransformed scores on the AP scales. AP_1-AP_4 = AP assessment wave 1 to 4; DZf = dizygotic female; DZm = dizygotic male; MZf = monozygotic female; MZm = monozygotic male; NA = not applicable; RI = Relative immaturity assessment wave 1.

Table S4. Twin Correlations Between Relative Immaturity (RI) and Attention Problems (AP) Across Ages, Presented by Rater, Sex, and Zygosity

Parent Ratings					
Male MZ twins: parent ratings					
	Twin 2				
Twin 1					
	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.89	0.35	0.27	0.23	0.18
AP 8-9		0.58	0.39	0.38	0.36
AP 13-14			0.65	0.37	0.33
AP 16-17				0.70	0.51
AP 19-20					0.67
Male DZ twins: parent ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.28	0.06	-0.02	0.00	0.09
AP 8-9		0.11	0.13	0.02	0.19
AP 13-14			0.21	0.10	0.27
AP 16-17				0.07	0.28
AP 19-20					0.36
Female MZ twins: parent ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.81	0.12	0.12	0.14	-0.04
AP 8-9		0.49	0.30	0.28	0.19
AP 13-14			0.57	0.41	0.28
AP 16-17				0.61	0.04
AP 19-20					0.52
Female DZ twins: parent ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.48	0.09	0.06	0.05	0.01
AP 8-9		0.33	0.22	0.35	0.15
AP 13-14			0.40	0.25	0.17

AP 16-17				0.40	0.37
AP 19-20					0.16
Opposite-sex DZ twins (female to male): parent ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.32	0.03	0.00	-0.06	-0.01
AP 8-9		0.31	0.22	0.30	0.19
AP 13-14			0.31	0.30	0.16
AP 16-17				0.33	0.13
AP 19-20					0.22
Twin self-ratings					
Male MZ twins: self-ratings					
	Twin 2				
Twin 1					
	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.89	na	0.18	0.11	-0.05
AP 8-9		na	na	na	na
AP 13-14			0.52	0.43	0.20
AP 16-17				0.52	0.32
AP 19-20					0.41
Male DZ twins: self-ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.31	na	0.08	-0.04	-0.05
AP 8-9		na	na	na	na
AP 13-14			0.40	0.22	0.19
AP 16-17				0.13	0.10
AP 19-20					0.10
Female MZ twins: self-ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.81	na	0.10	0.11	0.02
AP 8-9		na	na	na	na
AP 13-14			0.54	0.34	0.33
AP 16-17				0.44	0.32

AP 19-20					0.46
Female DZ twins: self-ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.48	na	0.01	0.04	-0.05
AP 8-9		na	na	na	na
AP 13-14			0.33	0.22	0.29
AP 16-17				0.27	0.24
AP 19-20					0.18
Opposite-sex DZ twins (female to male): self-ratings					
	Twin 2				
Twin 1	RI 8-9	AP 8-9	AP 13-14	AP 16-17	AP 19-20
RI 8-9	0.26	na	0.07	0.05	0.04
AP 8-9		na	na	na	na
AP 13-14			0.24	0.14	0.12
AP 16-17				0.17	0.16
AP 19-20					0.24

Note: Intra-class twin correlations presented on the diagonal, cross-twin, cross-trait (cross-time) correlations on the off-diagonal. Correlations were calculated using the raw, untransformed scores on the AP scales. DZ = dizygotic; MZ = monozygotic; NA = not applicable.

Table S5. Sensitivity Analysis for the *DSM*-Oriented Attention Problems (AP) Scale

Standardised Parameter Estimates With 95% CIs for the Best-Fitting AE Model and Percentage of Variance Explained in Latent Factors

		Genetic Parameter Estimates						Non-shared Environmental Parameter Estimates					
Factor/Age	Total h2 %	A1	A2	A3	A4	A5	Total e2 %	E1	E2	E3	E4	E5
RI/ 8-9 y old	86%	0.93 (0.91-0.94) 86%					14%	0.38 (0.35-0.41) 14%				
AP/8-9 y old	50%	0.24 (0.18-0.32) 6%	0.66 (0.61-0.85) 44%				50%	0.20 (0.13-0.30) 4%	0.68 (0.35-0.73) 46%			
AP/13-14 y old	70%	0.24 (0.17-0.31) 6%	0.50 (0.42-0.58) 25%	0.63 (0.55 -0.69) 40%			30%	0.22 (0.15-0.30) 5%	0.22 (0.15-0.40) 5%	0.45 (0.31-0.53) 20%		
AP/16-17 y old	63%	0.21 (0.13-0.29) 4%	0.53 (0.40-0.65) 28%	0.44 (0.32 -0.56) 19%	0.34 (0.17-0.49) 12%		37%	0.16 (0.08-0.24) 3%	0.11 (0.03-0.24) 1%	0.47 (0.35-0.59) 22%	0.34 (0.10-0.47) 12%	
AP/19-20 y old	82%	0.17 (0.08-0.26) 3%	0.56 (0.43-0.68) 31%	0.35 (0.20 -0.49) 12%	0.60 (0.31-0.69) 36%	0.00 (-0.50-0.50) 0%	18%	0.13 (0.01-0.25) 2%	0.08 (-0.03-0.33) 1%	0.37 (0.23-0.50) 14%	-0.14 (-0.32-0.05) 2%	0.00 (-0.28-0.28) 0%

Note: A1 to A5 and E1 to E5 show latent factors presented separately for genetic and non-shared environmental effects (Figure 1); 95% profile likelihood CIs are presented in parentheses. e2 = total proportion of variance explained by non-shared environmental factors; h2 = total proportion of variance explained by genetic factors; RI = relative immaturity.

Table S6. Sensitivity Analysis for the *DSM* Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Checklist

Standardised Parameter Estimates With 95% CIs for the Best-Fitting AE Model and Percentage of Variance Explained in Latent Factors

		Genetic Parameter Estimates						Non-shared Environmental Parameter Estimates					
Factor/Age	Total h2 %	A1	A2	A3	A4	A5		Total e2 %	E1	E2	E3	E4	E5
RI/ 8-9 y old	86%	0.93 (0.91-0.94) 86%						14%	0.38 (0.35-0.41) 14%				
AP/8-9 y old	78%	0.23 (0.17-0.28) 5%	0.85 (0.83-0.87) 72%					22%	0.10 (0.06-0.15) 1%	0.46 (0.43-0.49) 21%			
AP/13-14 y old	74%	0.20 (0.14-0.26) 4%	0.45 (0.39-0.49) 20%	0.71 (0.67-0.74) 50%				26%	0.13 (0.07-0.18) 2%	0.12 (0.07-0.16) 1%	0.48 (0.45-0.52) 23%		
AP/16-17 y old	73%	0.24 (0.18-0.30) 6%	0.43 (0.38-0.48) 18%	0.44 (0.38-0.49) 19%	0.54 (0.49-0.59) 29%			27%	0.07 (0.02-0.13) 0%	-0.01 (-0.06-0.05) 0%	0.11 (0.06-0.16) 1%	0.50 (0.47-0.54) 25%	
AP/19-20 y old	69%	0.12 (0.05-0.20) 1%	0.34 (0.27-0.41) 12%	0.32 (0.24-0.39) 10%	0.34 (0.25-0.43) 12%	0.59 (0.52-0.65) 35%		31%	0.09 (0.02-0.16) 1%	0.10 (0.04-0.17) 1%	0.15 (0.09-0.22) 2%	0.02 (-0.05-0.08) 0%	0.51 (0.47-0.56) 26%

Note: Parameter estimates were calculated using a standard Cholesky decomposition without rater-specific factors. A1 to A5 and E1 to E5 show latent factors of parent ratings only, presented separately for genetic and non-shared environmental effects; 95% profile likelihood CIs are presented in parentheses. AP = attention problems; e2 = total proportion of variance explained by non-shared environmental factors; h2 = total proportion of variance explained by genetic factors; RI = relative immaturity.

Figure S1. Standardized parameter estimates for best-fitting additive genetic and unique environmental (AE) model with no sex differences. Note: AP = attention problems.